FDA PMA P090012 Executive Summary

MELA Sciences, Inc.
MelaFind
November 18, 2010

FDA Executive Summary
November 18, 2010 Panel Meeting
of
General and Plastic Surgery Devices Panel

Introduction

This is the Executive Summary for Premarket Approval (PMA) application P090012 submitted by MELA Sciences, Inc. for a medical device named the MelaFind, a non-invasive and objective multi-spectral computer vision system designed to be used by physicians during assessment for biopsy of non-acral, non-ulcerated and non-bleeding pigmented cutaneous lesions that have diameter 2-22mm and are atypical due to at least one clinical characteristic of melanoma such as asymmetry, border irregularity, color variegation, regressing, evolving overtime, is causing patient concern or is an 'ugly duckling.' MelaFind has been reviewed by the General Surgery Devices Branch of the Division of Surgical, Orthopedic, and Restorative Devices at the Center for Devices and Radiological Health of the Food and Drug Administration.

This Executive Summary provides an overview of the information provided by MELA Sciences in P090012. This summary also provides the rationale for bringing P090012 to panel, an identification of the applicant/manufacturer, the proposed indications for use, and the FDA review team's summary of the device description, engineering testing, clinical study information, and labeling.

Rationale for Bringing P090012 to the General and Plastic Surgery Devices Panel

The FDA review team is presenting the PMA P090012 to the General and Plastic Surgery Devices Panel for panel deliberation of the safety and effectiveness of the MelaFind device based upon the results from the clinical study. The device is being taken to panel since MelaFind is a first of the kind device and the sponsor has requested a panel. *FDA may refer the PMA to a panel on its own initiative, and will do so upon the sponsor's request of an applicant, unless the FDA determines that the application substantially duplicates information previously reviewed by a Panel.*[1] The timing of this Panel as requested by the sponsor depends upon FDA review and assessment of the information preparedness.

The FDA review team seeks the Panel's input to determine whether the current data and/or studies are sufficient to support the risk benefit of the device for the MelaFind's proposed indications for use. The FDA review team will provide a history of the device application and a summation of the research protocols, and then provide its analysis of the data and remaining issues that will provide the basis for several questions to the advisory panel at the panel meeting.

[1] Code of Federal Regulations Title 21§814.44(a)

Table of Contents

Table of Contents

Table of Figures and Tables

Figure **Page Number**

Tables **Page Number**

Applicant/Manufacturer Information

Applicant/Manufacturer Name and Address:

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50 South Buckhout St.
Suite 1
Irvington, NY 10533
USA

Indications for Use

MelaFind® is indicated for the evaluation of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling"), when a physician chooses to obtain additional information before making a final decision to biopsy to rule out melanoma. MelaFind® is a non-invasive objective multi-spectral computer vision system designed as a tool to aid physicians in the detection of early (e.g., non-ulcerated, not bleeding, or less than 2.2 cm in diameter) melanoma.

MelaFind® is not a screening device and is not indicated for non-pigmented lesions, banal pigmented lesions, lesions that are clinically identified as definite melanomas, or lesions on special anatomic sites (i.e., acral, mucosal, subungual).

Device Description

MelaFind is a computer-controlled multi-spectral dermoscope that uses light, wavelengths from 430 nm (blue) through 950 nm (near infrared), to image the skin through a thin layer of liquid (alcohol or oil), making lesion structures under the skin surface visible to the observer. MelaFind is intended to be used by physicians during assessment of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling"), when a physician chooses to obtain additional information before making a final decision to biopsy to rule out melanoma.

Figure 1: Hand Held Imaging Device (Probe)

Figure 2: MelaFind System

MelaFind® provides a binary output: MelaFind® positive (= 1) and MelaFind® negative (= 2), the positive class is intended to consist of cutaneous malignant melanoma, high-grade dysplastic nevus (dysplastic nevus with severe atypia), and atypical melanocytic proliferation/hyperplasia[2], and the negative class is intended to consist of all other pigmented skin lesions.

[2]Atypical melanocytic proliferation/hyperplasia refers to new junctional nevi that may develop in elderly individuals and histologically often having features of early melanoma *in situ*. The sponsor references a paper:

Principles of Operation:

MelaFind System Workflow:

(1) Operator's enters patient data; (2) Operator removes or trims any hair from the lesion area, cleans area with alcohol, then squirts a few drops of 91% isopropyl alcohol over the lesion to be imaged; (3) The operator views the preview image and presses the trigger on the hand-held imaging device and holds it steady for 2-3 seconds (until a beep is heard and "Done" appears); (4) Software on the base computer checks that all hardware diagnostic status data are within normal operating ranges, and the probe then transfers the ten-band image to the base computer.; (5) Once an image is accepted, it is calibrated in each spectral band and then segmented, following which values are calculated for a set of lesion features. The computer sends a result message to the monitor, for display to the operator (6). This output provided is either "MelaFind POSITIVE" or "MelaFind NEGATIVE."

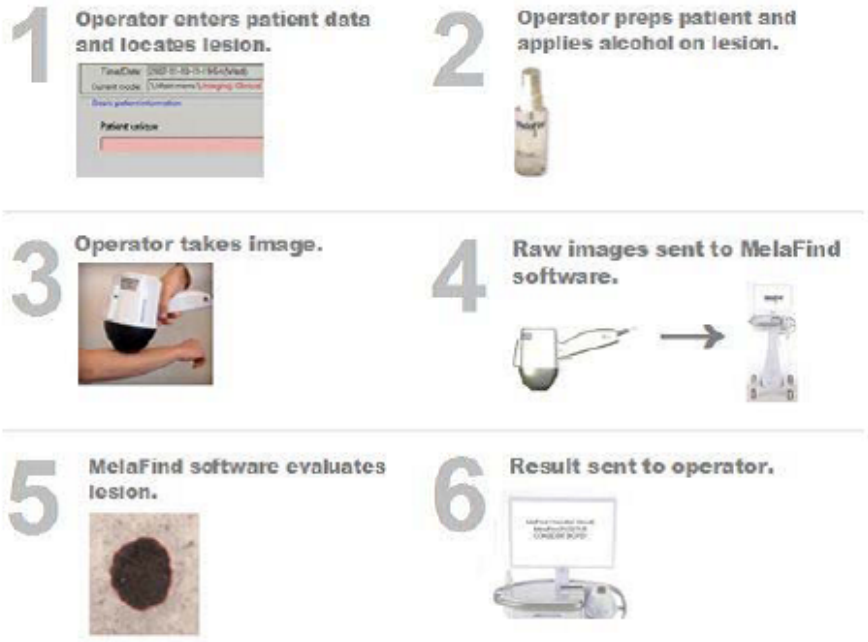

Figure 3: MelaFind Work Flow

Kossard S. Atypical lentigionous junctional nevi of the elderly and melanoma. Austalas J Dermatol 2002;43:93-101.

Engineering Testing:
Electrical Safety Testing:
The electrical safety of the device and its ability to function after exposure to environmental handling hazards was evaluated by the Underwriters Laboratories Inc. The sponsor states that they have conformed to the following EMC Standards:

- International Electrotechnical Commission (IEC) 60601-, 1st Edition 2006-04-26, C, Medical Electrical Equipment, Part 1: General Requirements for Safety;
- Underwriters Laboratory (UL) 2601-1 Amendment 1 Medical Electrical Equipment: General Requirements for Safety;
- AN/CSA-C22.2 No. 601.1-M90, 2005, IEC60601-1 (1998) 2nd edition with Amendment No.1 (1991) and No.2 (1995);
- American National Standards Institute (ANSI)/AAMI ES-1 Safe current limits for electromedical apparatus;
- IEC 60529 Degrees of protection provided by enclosures (IP Code) Consolidated Edition;
- IEC 60721-4-x TR (Technical Reports).

FDA review team finds this Engineering testing adequate and has no further questions.

Electromagnetic Compatibility (EMC) Testing:
The EMC of MelaFind was evaluated according to IEC 60601-1-2 Medical Electrical Equipment -- Part 1: General Requirements for Safety; Electromagnetic Compatibility -- Requirements and Tests (Second Edition, 2001) method.

A detailed report is provided in PMA Attachment 5-10: (CB) National Certification Body Report_E318009-A2-CB-1.

FDA review team finds this EMC testing adequate and has no further questions.

Hazard Analysis:
PMA Attachment 7-1: MF100 Risk Management Report provides a system Risk analysis summary for the entire MelaFind. In addition, a software hazard analysis is described in PMA Attachment 7-3: MF100 Software Design Specification. A detailed, worst-case analysis of the illuminator output hazard is provided in PMA Attachment 5-11: Output Characteristics of the MelaFind Illuminator and Comparison with ACGIHTLV.

FDA review team finds this analysis adequate and has no further questions.

Software Testing:
All components of the device are controlled/monitored by software, which is responsible for the functionality, user interface, safety checks and performance accuracy. This includes the hand-held imaging device and the image analysis software running on the PC.

- Level of Concern: Acceptable
- Software Description: Acceptable
- Device (including software) Hazard Analysis: Acceptable

- Software Requirements Specifications (SRS): Acceptable
- Architecture Design Chart: Acceptable
- Software Design Specification (SDS) : Acceptable
- Traceability: Acceptable
- Software Development Environment Description: Acceptable
- Verification and Validation Documentation: Acceptable
- Revision Level History: Acceptable
- Unresolved Anomalies (bugs): Acceptable

FDA review team has concluded that the sponsor has provided acceptable documentation demonstrating that they have developed the software for this device under an appropriate software development program; that they have performed a hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way.

Biocompatibility:
The sponsor states the materials used in the device that may come into contact with the patient or the operator device are procured from vendors who have certified these materials as meeting either the relevant ISO 10993 biocompatibility standard or the FDA version thereof. In general, these vendors have furnished test documentation demonstrating compliance.

FDA review team finds this adequate and has no further questions.

Sterilization:
Sterilization testing was not applicable since the patient contacting material, the probe, makes only short-term superficial skin contact with the patient.

FDA review team finds this adequate and has no further questions.

Manufacturing:
The manufacturing processes for the MelaFind cart and MelaFind System Integration consist of mechanical and electro-mechanical assembly processes for which the results are fully verified to meet requirements through inspection and/ or testing.

Table 1: MelaFind System Assembly Processes

PROCESS	VERIFICATION METHODS
Mechanical assembly – Cart and probe cases, housings, structure, wheels	Assembler inspection, QC inspection
Electro-mechanical assembly – Cart and probe electronics and cables	Assembler inspection, QC inspection, MelaFind Final Integration Test Procedure M100-TP-001
System integration – installation of system software, connection to probe	MelaFind Final Integration Test Procedure M100-TP-001

Reference:

- Drawings and selected assembly, test, and inspection procedures for the probe are provided in PMA Attachments 4-9 to 4-27.
- Drawings, and selected assembly, test, and inspection procedures for the cart assembly are provided in PMA Attachments 4-28 to 4-35.
- Top level specifications and selected assembly, test, and inspection procedures for the probe are provided in PMA Attachment 4.

FDA review team finds this adequate and has no further questions.

I – Summary of Clinical Studies

Mela Sciences, Inc. performed six clinical studies of MelaFind between November 2001 and July 2008 developing the device and the software. Five of these; Protocols 20011, 20012, RCP2007-05 (sponsored by L'Oreal) were the basis of Protocol 20031 and the FDA-Sponsor Protocol Agreement. The sponsor reports that Protocols 20031-A, and 20031-B were used to develop the automatic MelaFind® image analysis algorithms, which were studied in Protocol 20061 provided in the PMA P090012.

Table 2: Summary of Clinical Studies

Protocol No.	Protocol Title	Protocol Version Date	Dates of Accrual	MelaFind® System Configuration	Study Objectives	Use of Data
20011	Patient Examination with MelaFind™ System Developed by Electro-Optical Sciences, Inc. (EOS)	16-Apr-01	12-Apr-01 to 25-Jul-08	Portable Case/ Cart	To acquire data needed for the continuing development of MelaFind®	Development of MelaFind® image analysis algorithms
20012	Non-invasive Breslow Thickness Measurement for Cutaneous Melanoma with MelaMeter™	2-Aug-01	30-Nov-01 to 28-Jul-04	Portable Case	To acquire data needed for the continuing development of MelaFind® and associated MelaMeter™ software	Development of MelaFind® image analysis algorithms
RCP2007-05	Benign Pigmented Skin Lesions: Melanin Localization and Quantification with MelaFind®	11-Jun-07	26-Sep-07 to 14-Apr-08	Cart	To acquire data needed for the continuing development of MelaFind® and to investigate the feasibility of melanin localization and quantification from MelaFind® images of benign pigmented skin lesions	Development of MelaFind® image analysis algorithms
20031-A	Evaluation of Pigmented Skin Lesions with MelaFind® System	30-Aug-04	12-Nov-04 to 5-Jul-05	Cart with Clinical Cameras	To demonstrate that MelaFind is safe and effective, using sensitivity to melanoma and specificity as metrics*	Development of MelaFind® image analysis algorithms
20031-B	Pilot Roll-in Study for Protocol 20061: Evaluation of Pigmented Skin Lesions with MelaFind® System	30-Jan-06	20-Dec-06 to 14-Jul-08	Cart with Clinical Cameras	To allow users to gain experience with both MelaFind® and the study methodology, prior to being initiated on Pivotal Trial Protocol 20061, while acquiring data needed for the final development of MelaFind® image analysis algorithms	Final development of MelaFind® image analysis algorithms
20061	Evaluation of Pigmented Skin Lesions with MelaFind® System	19-Dec-05	31-Jan-07 to 7-Jul-08	Cart with Clinical Cameras	To demonstrate that MelaFind® is safe and effective, using sensitivity to melanoma and specificity as metrics	Prospective testing of MelaFind® image analysis algorithms

*Protocol 20031-A was originally designed as a prospective pivotal trial of MelaFind® and stopped. It was later amended to become Protocol 20031-B and designated as a roll-in study for Protocol 20061

The following is an in-depth description of the two main studies that the sponsor is using to support the current indication for use.

II – Protocol 20061 Clinical Study

Clinical Study Design:
This was a multicenter, prospective, blinded study. The sponsor submitted research evidence from the literature that a clinical diagnosis often does not match histopathological diagnosis, FDA agreed with a requirement, per the protocol agreement (note: information on this will be provided below in detail), that the diagnostic performance of MelaFind (sensitivity and specificity) would be evaluated using dermatopathology as the reference standard. Therefore, only lesions undergoing biopsy were evaluable for analyses of sensitivity and specificity end points of Protocol 20061.

The following information was used to develop the protocol agreement:

In Protocol 20061, lesions atypical for suspicion of melanoma (F1) given the clinical diagnosis "Melanoma" (F2) and "Melanoma cannot be ruled-out" (F3) are considered ***clinically positive***. Atypical and not-atypical lesions undergoing biopsy for "Non-Melanoma Concerns" (F5 and F7) are considered ***clinically negative***.[3] Accrual continued until there were at least 93 central dermatohistopathologically confirmed melanomas from the "Melanoma cannot be ruled-out" (F3) and "Not melanoma" (F4) categories to allow for statistically valid testing of the study hypothesis - the sensitivity of MelaFind is at least 95%, at the 95% confidence level.

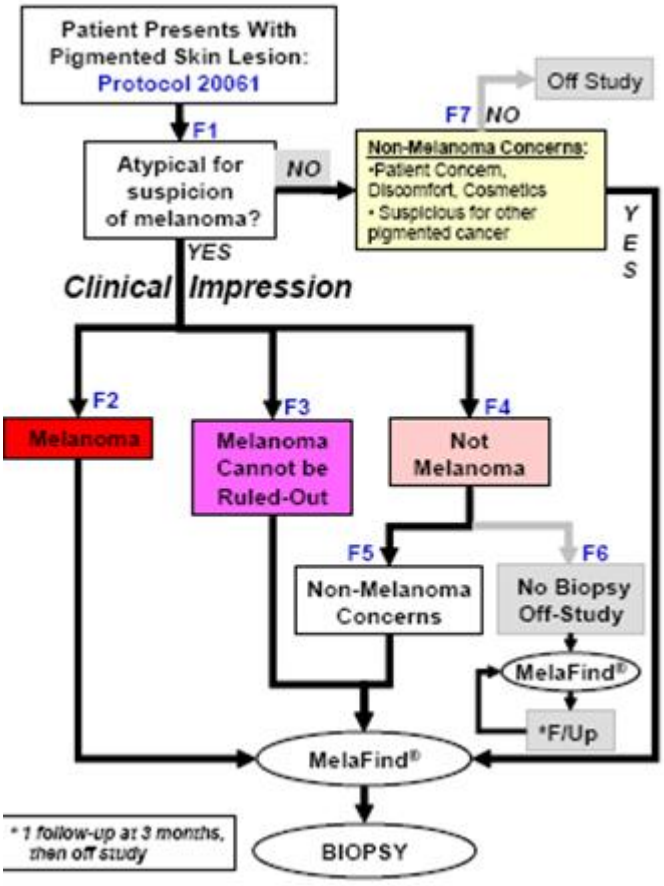

Figure 4: Population Schema

[3]The level of clinical expertise during the conduct of the study was by board-certified dermatologists with training for the evaluation of atypical skin lesions.

According to the sponsor, Protocol 20061 also evaluated the "Uncertain" category by drawing patients from the "Melanoma cannot be ruled-out" (F3) group, which represents the "Uncertain" lesions that were biopsied. Additional "Uncertain" lesions that were biopsied were derived from the "Non-Melanoma Concerns" (F5) category of the "Not Melanoma" group of atypical lesions (F4). The sponsor initially proposed that "Uncertain" lesions from the F4 "Not Melanoma" that are NOT biopsied would be followed (F6). However, no follow up group was enrolled. [FDA review team analysis: This group would have provided information on the collection of specific clinical, historical, and dermoscopic information that would have been useful in further characterizing the lesions in the "Uncertain" category. There will be additional discussion on this point in the clinical and statistical sections below.]

Protocol 20061 Primary Aim:

The studies primary aim was set to establish the safety and effectiveness of MelaFind, using sensitivity and specificity as metrics.

These are as described in A1 and A2 below:

- A1: To demonstrate that MelaFind's sensitivity to *malignant melanoma*, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is at least 95% at a 95% confidence level.
- A2: To demonstrate that, along with this high level of sensitivity, the specificity of MelaFind for lesions that are not malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is superior to the specificity of study dermatologists.

Inclusion Criteria that were used:

Cutaneous lesions examined with MelaFind had to satisfy all of the following inclusion criteria:

1. The lesion is pigmented (i.e., melanin, keratin, blood)
2. Clinical management of the lesion by the examining dermatologist is either:
   -Biopsy of the lesion *in toto*,
   OR -
   -3-month follow-up of the lesion
3. The diameter of the pigmented area is not < 2 mm, and not > 22 mm
4. The lesion is accessible to the MelaFind probe
5. The patient, or a legally authorized representative, has consented to participate in the study and has signed the Informed Consent Form

Exclusion Criteria:

Cutaneous lesions that meet any of the following exclusion criteria will not be accepted:

1. The patient has a known allergy to isopropyl alcohol
2. The lesion has been previously biopsied, excised, or traumatized

3. The skin is not intact (e.g., open sores, ulcers, bleeding)
4. The lesion is within 1 cm of the eye
5. The lesion is on mucosal surfaces (e.g., lips, genitals)
6. The lesion is on palmar hands
7. The lesion is on plantar feet
8. The lesion is on or under nails
9. The lesion is located on or in an area of visible scarring
10. The lesion contains foreign matter (e.g., tattoo, splinter, marker)

Selection of Patients that was utilized:
Upon evaluation of a patient presenting with one or more pigmented skin lesions, the examining clinician either decided to have a lesion(s) biopsied, or decided that a patient's lesion(s) should be evaluated again in 3 months, the patient became a prospective candidate for the clinical trial. (However, no patients were studied in this fashion, all atypical lesions were biopsied and none were followed. This point will be discussed in the clinical and statistical sections below.)

Study Plan:
Seven clinical study sites (three academic institutions and 4 community practices) with expertise in early melanoma detection and management of pigmented skin lesions participated in the study. All sites had board-certified dermatologists as primary investigators. Lesions included in this study had to meet specified inclusion/exclusion criteria. All the images and electronic Case Report Form (eCRFs) acquired in this study were stored on flash cards and sent to an independent Data Custodian to analyze the MelaFind images using software provided by EOS (Electro-Optical Sciences), and to determine its diagnostic performance; the results and eCRFs were then sent to an independent statistician. The clinical study sites sent histological slides to EOS to coordinate review by the central study dermatopathologists and to provide the reference standard to the biostatistician, who then analyzed the combined data. The examining clinicians were blinded to the MelaFind results, dermatopathologists were blinded to both the dermatological diagnoses and MelaFind results, and MelaFind was blinded to both dermatological and histological diagnoses.

(For additional information and details on Protocol 20061, please refer to Tab A-Pivotal Clinical Report)

III – Protocol 20061 Clinical Study Outcomes

This was a multicenter (7 sites), prospective, blinded study involving 1383 enrolled patients having 1831 pigmented skin lesions (PSLs). Of the enrolled patients, 1257 of these patients with 1632 lesions were eligible and evaluable. The lesions included in the analysis were 127 in-situ and malignant melanomas and 48 High-Grade Dysplastic Nevi (HGDN) or Atypical Melanocytic Proliferation/Atypical Melanocytic Hyperplasia (AMP/AMH) lesions.

Patient Demographics:

The following table shows the study demographics:

Table 3: Summary Demographics of All Enrolled Patients and of Patients with Eligible and Evaluable Lesions

Demographic		All Patients Enrolled (N = 1383)	Patients with Eligible and Evaluable Lesions (n = 1257)
Gender	Male	638 (46.1%)	575 (45.7%)
	Female	745 (53.9%)	682 (54.3%)
Age	Mean	48	47
	Std. Dev.	18.3	18.0
	Median	47	46
	Range	7 - 97	7 - 97
Race	White	1354 (97.9%)	1232 (98.0%)
	American Indian/Alaskan Native	0	0
	Black/African-American	4 (0.3%)	2 (0.2%)
	Asian/Pacific Islander	18 (1.3%)	17 (1.4%)
	Other	7 (0.5%)	6 (0.5%)
	Declined to Answer	0	0
Ethnicity	Hispanic or Latino	23 (1.7%)	20 (1.6%)
	Neither Hispanic nor Latino	1321 (95.5%)	1200 (95.5%)
	Other	27 (2.0%)	26 (2.1%)
	Declined to Answer	12 (0.9%)	11 (0.9%)

The 1257 patients consisted of 575 (45.7%) males and 682 (54.3%) females. The mean age was 47 years old (with STD=18 and range=7 to 97). Patients were mostly white (1232 or 98%).

The following table and text below describes the histological reference standard used:

Table 4: The Histological Reference Standard*

Lesion Type (n = 1632)	Lesion sub-type	n	%
Melanoma	127		7.8
	Invasive	70	4.3
	in situ	57	3.5
Atypical Melanocytic Hyperplasia/Proliferation	5		0.3
Nevus	1258		77.1
	Dysplastic, high-grade	43	2.6
	Dysplastic, low-grade	998	61.2
	Congenital/Congenital pattern	37	2.3
	Blue	16	1.0
	Spitz/Reed/Spindle Cell	10	0.6
	Other	154	9.4
Keratosis	119		7.3
	Seborrheic	93	5.7
	Solar/Actinic	16	1.0
	Other	10	0.6
Lentigo	76		4.7
	Solar/Actinic	31	1.9
	Other	45	2.8
Pigmented Basal Cell Carcinoma	23		1.4
Pigmented Squamous Cell Carcinoma	10		0.6
Other	14		0.9

*Results from dermatopathologist evaluation of biopsied lesions

Additional details on the histological reference standard for the 1632 eligible and evaluable lesions was as follows:

- Melanomas: 7.8% (total=127; melanoma invasive=70 and melanoma *in situ*=57)
- AMH/AMP: 0.3% (5)
- Nevus: 77.1% (1258)
- Keratosis: 7.3% (119)
- Lentigo: 4.7% (76)
- Pigmented Basal Cell Carcinoma: 1.4% (23)
- Pigmented Squamous Cell Carcinoma: 0.6% (10)
- Other: 0.9% (14)

<u>The following was the dermatological diagnosis of eligible and evaluable lesions (N=1632):</u>
Melanoma: 1.23% (20/1632)
Melanoma cannot be ruled out: 91.97% (1501/1632)
Not melanoma: 6.80% (111/1632)

<u>The following was the Breslow thickness of the eligible and evaluable invasive melanoma (N=70):</u>

Number of lesions < 1 mm: 68 (97.1%)
Number of lesions 1 – 2 mm: 2 (2.9%)
There were no lesions with more than 2 mm.

The following 2 x 2 schematic describes how the dermatopathology standard that was used to determine sensitivity and specificity:

Dermatopathology

MelaFind	Melanoma	Not Melanoma	Total
+	A (TP)	B (FP)	A+B
-	C (FN)	D (TN)	C+D
Total	A+C	B+D	N=A+B+C+D

True Positive (TP) = MelaFind calls positive and the lesion is dermatopathology positive for melanoma

False Positive (FP) = MelaFind calls positive and the lesion is dermatopathology negative for melanoma

False Negative (FN) = MelaFind calls negative and the lesion is dermatopathology positive for melanoma

True Negative (TN) =MelaFind calls negative and the lesion is dermatopathology negative for melanoma

For those lesions where the examining clinicians made the diagnosis of "Melanoma cannot be ruled out" or "Not melanoma," the sensitivity of MelaFind is calculated as: TP/(TP+FN) (=A/(A+C)) where TP are cases where MelaFind returned a positive reading and malignant melanoma by central dermatopathology and TP+FN= all cases where central dermatopathology review returned a diagnosis of melanoma.

Primary Aim Outcomes:

For the primary aim, only 1612 lesions were used because 20 of the 1632 eligible and evaluable lesions received a clinical diagnosis "Melanoma". According to **Protocol Agreement, Point 3**, these 20 lesions must be excluded from the primary analysis. Of the 1612 remaining lesions, 114 lesions were then as biopsy diagnosed as melanomas.

Sponsor's Outcomes of Primary Aim A1:
To demonstrate that MelaFind's sensitivity to malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is at least 95% at a 95% confidence level.

Outcome: MelaFind sensitivity = 98.25% (112/114); 95% Lower confidence bound (LCB) = 95.1%

The statistical method the sponsor used for obtaining an exact 95% LCB of 95.1% is the "mid-P exact method." Before choosing the mid-P exact method for this analysis, the sponsor considered carefully the anticipated sample size and likely values for the estimated proportion, as well as the properties of available inferential methods. This

consideration is particularly important when the proportion being estimated is close to the extremes of the parameter space (i.e., very close to 100%). The sponsor chose the mid-P exact method to be the most appropriate when estimating the 95% LCB for sensitivity in Protocol 20061.

In PMA P090012 Section 2.3 Statistical methods, subsection 2.3.5.1 Primary Aim A1 (page 20), the sponsor states:

> *Uncertainty in the estimate of sensitivity of MelaFind® was quantified using a one-sided 95% exact lower confidence bound (LCB). The mid-P exact [7,8,9] method is based on the binomial distribution, and was used because of small sample size and because we anticipated sensitivity close to the boundary of the parameter space.*

References:
6. Agresti A, Coull B. Approximate is better than "exact" for interval estimation of binomial proportions. American Statistician, 52:119-126 (1998).
7. Agresti A, Gottard A. Randomized confidence intervals and the mid-P approach. Statistical Science 20(4):367-371 (2005).
8. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine 17(8):857-872 (1998).
9. Vollset SE. Confidence intervals for a binomial proportion. Statistics in Medicine 12(9):809-24 (1993).

FDA Review Team's Outcomes of Primary Aim A1:

The following are the 95% two-sided and one-sided confidence intervals for sensitivity = 98.25% (112/114) by the Clopper-Pearson, Score, and midP methods:

Table 5: Statistical Methods used in Analysis for Protocol 20061

Method	**95% two-sided CI**	**95% one-sided CI**
Clopper-Pearson	93.8% to 99.8%	94.6% to 100.0%
Score	93.8% to 99.5%	94.8% to 100.0%
midP	94.4% to 99.7%	95.1% to 100.0%

The sponsor used the midP method to compute a one-sided 95% confidence interval (CI) on sensitivity. In contrast, if the Clopper-Pearson or Score method is used instead of midP, the LCB is slightly less than 95%, indicating that primary aim A1 was not met. However, both alternative LCBs round to 95% and all three methods give similar results. Rather than focus on the binary decision of whether primary aim A1 was met or not, all of the analysis methods can be said to show borderline significant results for sensitivity being greater than 95% using a one sided test.*

The Clopper-Pearson method guarantees that the one-sided 95% confidence interval has at least 95% coverage, but can be conservative due to the discreteness of count data. Neither the Score method nor the mid-P method guarantees 95% coverage for all values of a proportion. Over all values, on average the mid-P method provides about 95% coverage and is less conservative than the Clopper-Pearson method [6,9].

An investigation of the coverage of each the three methods was given in [9]. For a sample size of 100 (close to the study sample size of 114 melanoma lesions), the two-sided 95% confidence intervals generated by the midP and Score methods may not have the nominal 95% coverage when the true value of the proportion is between 0.9 and 0.99, while Clopper Pearson always does (see figures below, reprinted from [9]).

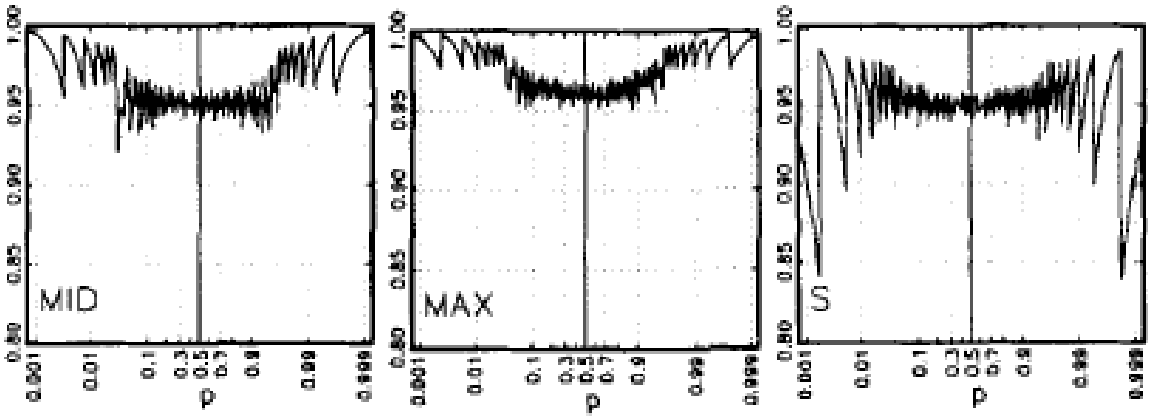

Figure 5: Coverage probabilities of MidP (MID), Clopper-Pearson (MAX), and Score (S) two-sided 95% confidence intervals. Reprinted from Vollset (1993).

*The latest guidance issued by FDA on March 13 2007, "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests," recommends reporting two-sided 95% confidence intervals. The Score method is used as an example in this Guidance. It should be noted that the agreement with the sponsor on the study design and analysis plan for MelaFind occurred before the FDA guidance was finalized.[4]

Sponsor and FDA Review Team's Outcome of Primary Aim A2:
To demonstrate that, along with this high level of sensitivity, the specificity of MelaFind for lesions that are not malignant melanoma, among lesions with dermatological diagnoses of "Melanoma cannot be ruled out" or "Not melanoma", is superior to the specificity of study dermatologists.

The following is an estimate of the average MelaFind specificity and the average dermatologist specificity from a model with study investigator (dermatologist) as a random effect. The 95% confidence interval on the difference in specificity accounts for correlations arising from interpreting the same lesions with both modalities:

[4] Please see also page 46 of this Executive Summary regarding Protocol Agreement concerns.

Outcome: MelaFind specificity = 9.49% and study examining dermatologist's specificity = 3.71%; (difference in specificity = 5.78, 95% CI : 0.92-10.64, p-value for difference in specificities = 0.022)

Alternatively, the observed specificity of MelaFind when all lesions are pooled together is provided along with its 95% Bootstrap confidence interval, which accounts for correlation among results for multiple lesions from the same patient:

Outcome: MelaFind Specificity = 10.55% (158/1498) (95% CI: 8.9% to 12.2%)

The model-based and pooled estimates of MelaFind specificity differ. The random effects model effectively took a straight average of the per investigator MelaFind specificities, whereas the pooled estimate weights these specificities, where the weight is proportional to the number of lesions the investigator examined.

(For Secondary Aim Outcomes, please refer to Sponsor's Analysis, Tab A page 42)

The following page is a summary table of the results from this study:

Table 6: Protocol 20061-Summary of Data

Clinical Assessment Group			Population						All Pigmented Lesions
			Atypical				Not Atypical		
			Melanoma (F2)		Melanoma Cannot Be Ruled Out (F3)		Not melanoma (F4)		Non-atypical pigmented lesion (F7)	All Populations
N, Lesions from Patients Enrolled			25		1702		103		1	1831
Gender*	Female		11		920		61		1	993
	Male		14		782		42		0	838
Age*	< 21 years		0		102		5		0	107
	21 - 55 years		13		1082		46		1	1142
	> 55 years		12		518		52		0	582
Anatomic Location*	Face		1		51		7		0	59
	Posterior Torso		7		745		34		1	787
	Anterior Torso		0		358		18		0	376
	Extremity: Arm/ Leg		16		491		50		0	557
	Neck		0		32		8		0	40
	Scalp		1		25		6		0	32
Fitzpatrick Skin Type*	I		3		112		2		0	117
	II		11		897		73		0	981
	III		8		610		24		0	642
	IV		3		75		3		1	82
	V		0		5		1		0	6
	VI		0		3		0		0	3
Geographic Sites**, Patients*	US - sun belt		22		1349		88		0	1459
	US - non-sun belt		3		353		15		1	372
	Non - US		0		0		0		0	0
N, Lesions Enrolled			25		1702		103		1	1831
N, Lesions Biopsied			25		1702		103		1	1831
N, Eligible and Evaluable Lesions			20		1528		83		1	1632

Lesion				Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	Is MM/HGDN/ AMP/AMH	Is not MM/HGDN/AMP/ AMH	All Diagnoses
N, Number of Lesions	By Physician (MD)			20	NA	1528	NA	NA	83	NA	1	1632
	By MelaFind (MF)			20	0	1385	145	68	15	1	0	1632
	By Dermatopathology (DP)			14	6	159	1369	2	81	0	1	1632
	Dermatopathology (DP)	Melanoma Type	in situ	4	NA	52	NA	1	NA	0	NA	57
			invasive	9	NA	61	NA	0	NA	0	NA	70
		Melanoma Breslow Thickness	< 1 mm	8	NA	60	NA	0	NA	0	NA	68
			1 - 2 mm	1	NA	1	NA	0	NA	0	NA	2
			2.1 - 4 mm	0	NA	0	NA	0	NA	0	NA	0
			> 4 mm	0	NA	0	NA	0	NA	0	NA	0
		HGDN		1	NA	41	NA	1	NA	0	NA	43
		AMP/AMH		0	NA	5	NA	0	NA	0	NA	5
		Dysplastic nevi, low grade		NA	5	NA	978	NA	15	NA	0	998
		Other nevi		NA	0	NA	189	NA	28	NA	1	218
		Non-melanoma skin cancers		NA	0	NA	23	NA	10	NA	0	33
		Other non-melanocytic lesions		NA	1	NA	179	NA	28	NA	0	208
	by DP & MD & MF			NA	0	NA	0	NA	15	NA	0	15
	by DP & MD & not MF			NA	0	NA	0	NA	66	NA	1	67
	by DP & MF & not MD			NA	0	NA	142	NA	0	NA	0	142
	by DP & not MF & not MD			NA	6	NA	1227	NA	0	NA	0	1233
	by DP & MD			NA	0	NA	0	NA	81	NA	1	82
	by DP & MF			14	0	156	142	2	15	0	0	329

*Cell counts are number of lesions. Patients who contributed more than one lesion to the study are represented in more than one population when those lesions occur in more than one population.

**Geographic sites were tabulated based on clinical study site. US - sun belt included Alabama, California, Florida, and North Carolina. US - non-sun belt included Pennsylvania and Illinois. All clinical study sites were in the US.

			Melanoma (F2)	Melanoma Cannot Be Ruled Out (F3)	Not melanoma (F4)	Non-atypical pigmented lesion (F7)	All Populations
		Sensitivity	100.0% (14/14)	98.1% (156/159)	100.0% (2/2)	NA	98.5% (172/175)
		Specificity	0.0% (0/6)	10.4% 142/1369)	18.5% (15/81)	0% (0/1)	10.8% (157/1457)
		PPV	70.0% (14/20)	11.3% (156/1383)	2.9% (2/68)	0.0% (0/1)	11.7% (172/1472)
		NVP	NA	97.9% (142/145)	100.0% (15/15)	NA	98.1% (157/160)
	Change in #correct diagnosis		0/20 in F2	3/1538 = 0.20% missed by MF	2/83 = 2.4% additional by MF		

IV. Protocol 20063 Clinical Study:

Clinical Study Design:

This was an on-line reader study (Protocol 20063) designed by the sponsor without the FDA review team's formal feedback. The sponsor's purpose was to evaluate the diagnostic and biopsy/referral performance of three groups of physicians (pigmented skin lesion experts, general dermatologists, and primary care physicians) and compare it with the performance of MelaFind.

The sponsor's primary aim of this study was to determine whether MelaFind's sensitivity was at least as good as the average biopsy/referral sensitivity of dermatologists. Additional aims were to compare MelaFind's sensitivity to that of physicians in different groups, to compare the performance among different physician groups using point estimates (sensitivity and specificity) and ROC analysis (area under the curve, AUC), and to quantify the level of interobserver variability within physician groups.

Materials and Methods

The study was an internet-based survey displaying high resolution digital images and corresponding full case histories for 130 pigmented skin lesions at a 1:1 melanoma to non-melanoma ratio; MelaFind result was not provided. Lesions for this study were randomly selected from the MelaFind pivotal trial database of eligible and evaluable cases, subject to image quality review by the Medical Director. Non-melanomas were further constrained to match the observed frequency of different histologic types in the entire database. Melanomas in this study were deemed to be early lesions by the sponsor, with the median Breslow thickness for invasive melanomas of 0.39 mm; 60% of non-melanomas were low-grade dysplastic nevi. The NIH Consensus Development Conference Statement on Diagnosis and Treatment of Early Melanoma, January 27-29, 1992 defines early melanoma as follow: melanoma in situ and thin invasive lesions less than 1 millimeter in depth and does not define early melanoma as non-ulcerated, not bleeding, or less than 2.2 cm in diameter as the sponsor proposes.

Physicians were randomly selected from various physician membership lists across the country and were invited to participate in this study by a third-party vendor, Embryon. About one tenth of those invited decided to participate in the study. Physicians were asked to complete an on-line Intake Survey, which was used to determine provider status. For each case reviewed, physicians were asked if they thought the lesion was a melanoma (diagnostic sensitivity/specificity) and whether or not they would biopsy or refer the lesion (biopsy/referral sensitivity/specificity). Only the biopsy/referral sensitivity / specificity of physicians were compared to MelaFind's sensitivity / specificity, since MelaFind provides a single binary output, and the biopsy decision governs patient management.

Aims:

Aim 1: To determine and compare the biopsy/referral sensitivity and specificity of MelaFind to the average biopsy/referral sensitivity and specificity of dermatologists. Dermatologists will consist of pigmented skin lesion experts and general dermatologists. The sponsor's hypothesis was that MelaFind has biopsy/referral sensitivity at least as good as the average of dermatologists using photographic images.

Aim 2: To compare the biopsy/referral sensitivity and specificity of MelaFind to the average biopsy/referral sensitivity and specificity in each of three groups of physicians: pigmented skin lesion experts, general dermatologists, and primary care physicians (PCPs).

Aim 3: To compare biopsy/referral performance and diagnostic performance using areas under the corresponding receiver operating characteristic (ROC) curves that illustrate the trade-offs between sensitivity and specificity between three groups of physicians: pigmented skin lesion experts, general dermatologists, and primary care physicians. We will also compare sensitivity and specificity independently.

> **Sub Aim 3.1:** To determine the interobserver variability in each of the above metrics within each caregiver group.

(For complete Protocol 20063 Protocol, please refer to Tab B)

V – Protocol 20063 Clinical Study Outcomes

Table 7: Characteristics of study lesions

Lesion characteristic	*Melanoma N=65 n (%)*	*Non-melanoma N=65 n (%)*	*Total N=130 n (%)*
Lesion location			
Head/neck	21 (32)	20 (31)	41 (32)
Trunk	20 (31)	22 (34)	42 (32)
Upper limbs	14 (22)	12 (18)	26 (20)
Lower limbs	10 (15)	11 (17)	21 (16)
Patient expressed concern about lesion[a]	**27 (42)**	**27 (42)**	**54 (42)**
The lesion has evolved[a]	**34 (52)**	**22 (34)**	**56 (43)**
Patient first noticed			
Less than 3 months	9 (14)	4 (6)	13 (10)
3 months to 1 year	11 (17)	6 (9)	17 (13)
More than 1 year	16 (25)	26 (40)	42 (32)
Never noticed	24 (37)	27 (42)	51 (39)
Unknown	5 (8)	2 (3)	7 (5)
Lesion changed since first noticed[b]	**26/33 (79)**	**19/30 (63)**	**45/63 (71)**
Size	18 (55)	13 (43)	31 (49)
Color	17 (52)	6 (20)	23 (37)
Shape	3 (9)	1 (3)	4 (6)
Border	0	2 (7)	2 (3)
Other change	0	1 (3)	1 (2)

Denominators and column headers are the total number of lesions.
a. According to the evaluating physician.
b. According to the patient. Denominators for this section are the number of lesions for which patients answered yes or no to "Has the lesion changed at all since it was first noticed?".

Patient and Study Physician Demographics:

Characteristics of study patients:

124 patients presented with these 130 lesions. Approximately half (48%) of the patients presenting with study lesions were male, and the average age was 55 years (SD = 22 years). Twenty-one percent (21%) had a personal history of melanoma.

Characteristics of study physicians:

Participating study physicians were required to complete an Intake Survey prior to accessing the survey study. The survey asked each physician for details about his or her medical practice and comfort with biopsy and the use of dermoscopy. The answer to the question "Time spent on pigmented skin lesions" was used to categorize dermatologists into general dermatologists (< 25%) and pigmented skin lesion experts (≥ 25%). The 155 eligible and evaluable physicians comprised 45 PCPs, 46 general dermatologists, and 64 PSL experts. Median years practicing was 15 for PCPs, 12 for general dermatologists, and 10 for PSL experts (10 for dermatologists combined). PCPs were predominantly family practitioners (42/45 = 93%), and most physicians in each group were in private practice (38/45 = 84% of PCPs, 38/46 = 83% of general dermatologists, 61/64 = 95% of PSL experts). As anticipated, fewer PCPs (6/45 = 13%) used dermoscopy compared with general dermatologists (20/46 = 43%) and PSL experts (32/64 = 50%).

The following section provides the **Aim results** provided by the sponsor.

Sponsor's Aim Outcomes:
Aim 1: *To determine and compare the biopsy/referral sensitivity and specificity of MelaFind to the average biopsy/referral sensitivity and specificity of dermatologists.*

Outcome: MelaFind's sensitivity (0.97) was higher than the average sensitivity for study dermatologists (0.72; difference = 0.25). MelaFind's specificity (0.09) was significantly lower than the average specificity for study dermatologists (0.52, difference=-0.41; 95% CI for difference = -0.51 to -0.31).

Aim 2: *To compare the biopsy/referral sensitivity and specificity of MelaFind to the average*
biopsy/referral sensitivity and specificity in each of three groups of physicians: pigmented skin lesion experts, general dermatologists, and primary care physicians.

Outcome: MelaFind's sensitivity (0.97) was higher than the average sensitivity for PCPs (0.71, difference=0.26; 95% CI for difference = 0.19 to 0.34), general dermatologists (0.73, difference=0.24; 95% CI for difference = 0.16 to 0.31), and PSL experts (0.71,difference=0.26; 95% CI for difference = 0.19 to 0.33). MelaFind's specificity (0.09) was lower than the average specificity in any study group (0.45 for PCPs, 0.51 for general dermatologists, and 0.50 for PSL experts).

The pairs of biopsy / referral sensitivities and specificities for the study physicians and for MelaFind are summarized in the following figure:

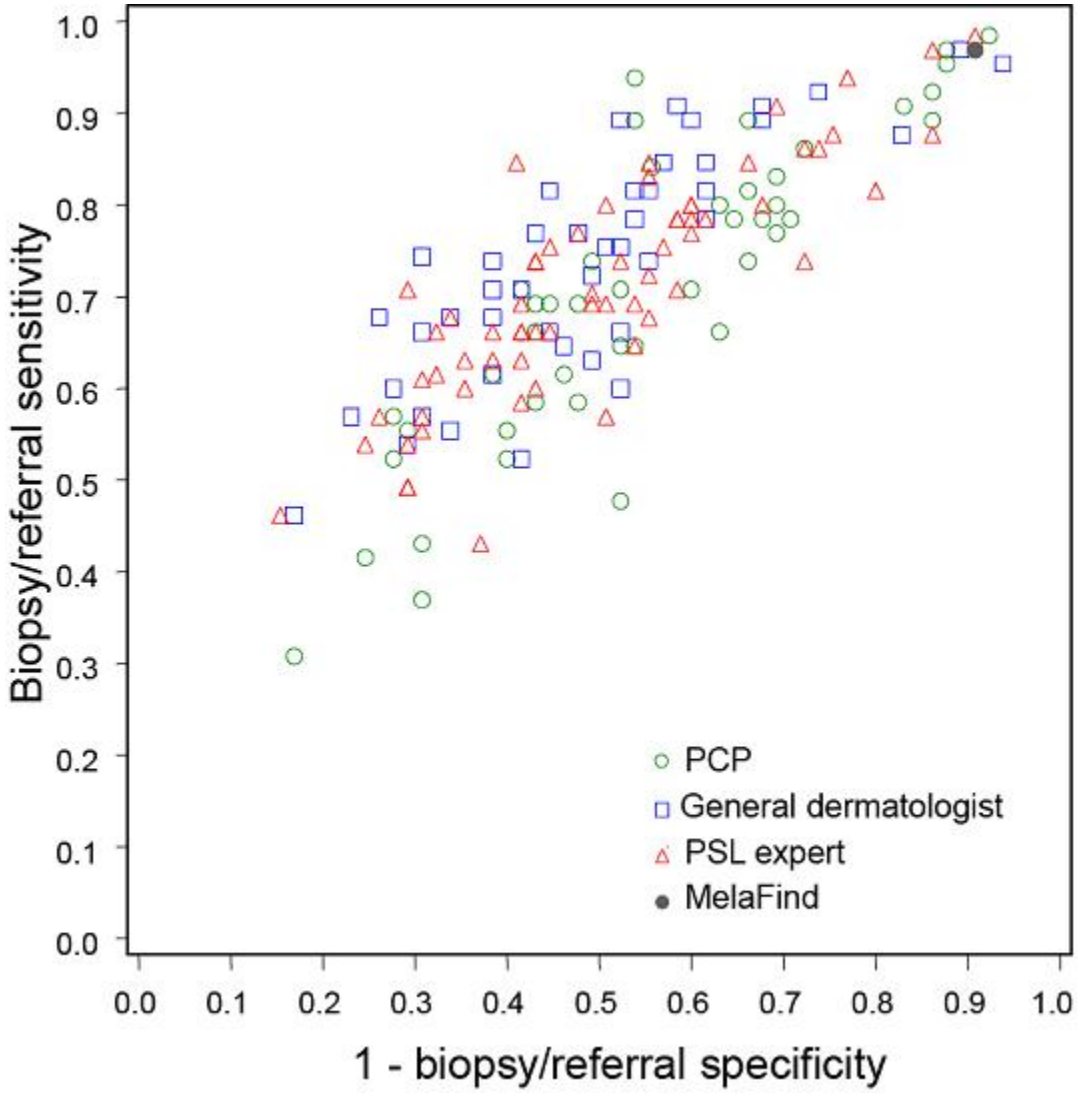

Figure 6: Plot of Biopsy/Referral Sensitivity Versus 1-Biopsy/Referal Specificity.

Aim 3: *To compare biopsy/referral performance and diagnostic performance using areas under the corresponding receiver operating characteristic (ROC) curves that illustrate the trade-offs between sensitivity and specificity between three groups of physicians: pigmented skin lesion experts, general dermatologists, and primary care physicians. We will also compare sensitivity and specificity independently.*

Sub Aim 3.1: *To determine the interobserver variability in each of the above metrics within each caregiver group.*

For Aim 3, The ROC curve is a plot of all pairs of sensitivity and 1 – specificity that can be produced by a continuous or ordinal valued test. If the observed value is above a cut-off, then the test result is positive, else it is negative. The cut-off is varied across the range of possible values to produce the ROC curve. For study 20063, physicians were asked to select the likelihood that this lesion should be sent for biopsy/referral (Scale of 0-10, 0 being "absolutely would biopsy" and 10 being "absolutely would not biopsy") and they were also asked to select a likelihood that a lesion is a melanoma (Scale of 0 - 10, 0 being "definitely

not melanoma," and 10 being "definitely melanoma"). These two scales were used to produce the AUC of ROC curve one for biopsy/referral and other for diagnosis of melanoma.

Outcome: Areas under the ROC curve (AUCs) for biopsy/referral for each of the three groups of physicians (AUC for PCP 0.59; GD 0.65; PSL 0.63) tended to vary across physicians less than sensitivity (PCP 0.71; GD 0.73; PSL 0.71) and specificity (PCP 0.45; GD 0.51; PSL 0.50) did, which was anticipated because AUCs include information from both melanomas and non melanomas in a single measure. Biopsy/referral AUCs tended to be lower for PCPs (0.59) than for general dermatologists (0.65) or PSL experts (0.63). General dermatologists and PSL experts tended to have higher specificities and AUCs than did PCPs. The smaller between-physician variance in AUCs allows that difference in performance to reach statistical significance, as evidenced by 95% CIs that exclude zero ($p < 0.05$ for general dermatologists vs PCPs and for PSL experts vs PCPs). Diagnostic sensitivities (PCP 0.43; GD 0.45; PSL 0.40) for each group of physician readers tended to be lower than biopsy/referral sensitivities and were highly variable in all three groups. Diagnostic specificities (PCP 0.71; GD 0.79; PSL 0.81) for each group of physicians were also highly variable. Diagnostic specificities tended to be higher than biopsy/referral specificities. Results are heterogeneous across study physicians and do not appear to aggregate by physician group. Physicians tended to value sensitivity over specificity when making the decision to biopsy/refer, whereas they tended to be more specific than sensitive when faced with the diagnostic task of deciding whether to classify a lesion as melanoma. As with biopsy/referral AUCs, there is less between-physician variability in diagnostic AUCs for each group of study physicians than for sensitivity or specificity; and diagnostic AUCs tended to be lower for PCPs than for general dermatologists and PSL experts. General dermatologists tended to perform better than PCPs in terms of diagnostic specificity and AUC; the same is true for PSL experts compared with PCPs. The smaller between-physician variance in AUCs allows that difference to reach statistical significance, as evidenced by 95% CIs that exclude zero ($p < 0.05$ for general dermatologists vs PCPs, and for PSL experts vs PCPs).

VI – FDA Review Team's Review of the Protocol Agreement

The FDA review team has provided this review of the protocol agreement and additional information on the studies involved to give some history to the Panel on how the assessment of the device changed since 2004 when FDA and the sponsor had an Agreement Meeting.

Having a background may help the panel in interpreting the results submitted for this meeting, and the FDA review team will outline also some concerns with these results and indications for use that have developed that are potentially relevant to the current indications for use and how this device may be used in clinical practice. [Note that as described below the FDA review team does not believe that the Protocol Agreement and data results support the proposed indications for use since there have been modifications of the study, especially the modification of not including or having a 3-month follow up Group (F6) with lesions that were to be followed prospectively.

1 – Prior to Agreement:

During discussions with the sponsor leading up to the Protocol Agreement, the sponsor proposed to have a 3-month follow up Group (F6) for those atypical lesions not selected for biopsy. The sponsor presented Protocol 20031: a non-randomized, prospective, multi-center clinical study to evaluate the safety and effectiveness of MelaFind. MelaFind was intended to aid dermatologist assessment of atypical lesions suspicious of melanoma before final decision to biopsy has been rendered to rule out melanoma.

The Primary Aims (Sensitivity and Specificity) and the decision steps in current practice **(Figure 4: Population Schema, pg 14)** of the Protocol Agreement were established to support MelaFind's claim to rule-out melanoma in atypical lesions suspicious of melanoma to reduce the number of unnecessary biopsies. However, in the absence of clinical data, FDA and the sponsor could not decide upon a mutually agreeable proposed indications for use for the agreement meeting.

2 – Agreement:

On October 20, 2004, FDA and the sponsor signed a Protocol Agreement based on Clinical Protocol 20031 and the following points:

Protocol Agreement:

1. The study inclusion and exclusion criteria are appropriate as described in Protocol 20031, dated August 30, 2004 ("Protocol 20031" hereinafter), on pp. 14 – 21.
2. Sensitivity and specificity as primary endpoints are appropriate metrics for evaluating the safety and effectiveness of MelaFind®
3. The population (F3 and F4 in figure 4 on page 16) of lesions/patients that will be included in the primary analysis - i.e., lesions receiving clinical diagnoses of "Melanoma cannot be ruled-out" and "Not melanoma" - are appropriate for evaluating the sensitivity and specificity of MelaFind when a final decision to biopsy has not been made by the study physician.

4. a. The sample size -93 dermatohistopathologically-confirmed melanomas among lesions receiving dermatological diagnoses of either "Melanoma cannot be ruled out" or "Not melanoma", with a minimum total number of lesions of 1200 – is sufficient for evaluating the sensitivity and specificity of MelaFind to correctly identify malignant melanoma.
4. b. In particular, that 93 such melanomas are sufficient to provide 80% probability that the 95% exact binomial lower confidence bound for sensitivity of MelaFind to correctly identify malignant melanomas in lesions receiving these dermatological diagnoses will exceed 0.95, when the expected sensitivity is (0.5)^(1/106) = 0.9935.
5. The central dermatopathology procedures and algorithm for final interpretation of biopsy specimens are an acceptable reference standard for establishing "ground truth" for the determination of sensitivity and specificity.
6. a. Standard clinical and dermoscopic photographs of lesions acquired using digital cameras provided by EOS are acceptable for capturing visual information on lesions entered into the study for future reporting and analysis.

6 b. Photographic requirements will be standardized for all clinical sites, and specific as to lighting, distance and angle from photographic site, camera resolution. Standardized rulers will be used by all sites, and placed next to the lesion prior to photography.

7. Clinical and historical data will be provided on all patients who sign an informed consent document.
8. An analysis of all data for patients in group F2 will be included in the submission.
9. The classifier will be fixed prior to analysis of the data from protocol 20031.

This agreement also stated that, *The agreement decision is binding on both the Center for Devices and Radiological Health (CDRH) and the sponsor. It can be changed only with the written agreement of the sponsor or when there is a substantial scientific issue essential to determining the safety or effectiveness of the device.*

It should be noted to the Panel that the Protocol Agreement will evaluate MelaFind performance, which is the evaluation of sensitivity and specificity. Sensitivity and specificity were recognized as appropriate metrics for evaluating safety and effectiveness, however, the protocol agreement was not designed to evaluate safety and effectiveness in clinical use. Medical devices are evaluated for market on the basis of device safety and effectiveness when used as intended in the target population, under the labeled conditions of use.

3 – Deviations/Modifications to the Protocol:

The clinical protocol followed and supplied by the sponsor in PMA P090012 was 20061 and not Protocol 20031. The sponsor states that clinical protocol 20031 served as a roll in protocol to capture lesion images. In addition, the device's positive detection algorithm was changed in Protocol 20031 to increase sensitivity for Protocol 20061. The sponsor has stated that the inclusion & exclusion criteria, methods, and central dermatopathology procedures of Protocol 20031 are identical to Protocol 20061, which

was reviewed by the FDA review team and found adequate for the original intent of ruling out melanoma to reduce unnecessary biopsies.

During the clinical study the sponsor also deviated from Protocol 20061 by not enrolling atypical lesions suspicious of melanoma in the 3-month follow-up group (F6). The sponsor indicated that the study investigators, who were board-certified dermatologists, were unwilling to defer biopsy in toto on the enrolled atypical lesions suspicious for melanoma and wait for three months between the first examination and a second examination at which time a biopsy would be taken stating that when the clinical study was actually initiated the standard of care was to biopsy in toto all atypical lesions suspicious of melanoma. Thus, no lesions were enrolled in the 3-month follow up group (F6).

4 – Issues Developing from Changes or Modifications to the Protocol:
The FDA review team believes therefore that the sponsor did not meet Point 1 of the FDA-sponsor agreement:

> ***Point 1:** *The study inclusion and exclusion criteria are appropriate as described in Protocol 20031, dated August 30, 2004 ("Protocol 20031" hereinafter), on pp. 14 – 21.*
>
> *Clinical management of the lesion by the examining dermatologists is either:*
>
> *-- Biopsy of the lesion in toto,*
> *-- OR –*
> *-- 3-month follow-up of the lesion"*

***Please refer to page 14 Figure 4: Population Schema and page 15 for inclusion criteria**

The 3-month follow up group (F6) was designed to provide additional data to evaluate whether MelaFind was able to effectively rule-out melanoma from the "Not Melanoma" (F4) Group by comparing the MelaFind result to the dermatologist's decision to defer immediate biopsy for a 3 month follow-up. The FDA review team and the sponsor would have had additional data to help determine if MelaFind could safely and effectively rule-out melanoma to reduce unnecessary biopsies in atypical lesions suspicious of melanoma.

The FDA review team believes the sponsor changed their intent from the detection of melanoma in *only atypical lesions suspicious for melanoma* as agreed upon **Figure 4: Population Schema (pg 14)** of the Protocol Agreement, to include *all atypical lesions (suspicious and non-suspicious for melanoma).*

The FDA review team believes that the clinical data in Protocol 20061 does not support MelaFind use for *the detection of early melanoma* on all atypical lesions (suspicious and non-suspicious for melanoma) since the data is limited to the enrolled atypical lesions suspicious for melanoma. In doing so, the FDA review team also believes the sponsor did not adhere to original intent of the Protocol Agreement which studied MelaFind on **only** atypical lesions suspicious for melanoma to rule-out melanoma in order to reduce

the number of unnecessary biopsies and not on all atypical lesions (suspicious and non-suspicious for melanoma).

5 – Sponsor's Response to these Concerns:
In regards to meeting Point 1 the Protocol Agreement regarding the exclusion of the 3-month follow up group (F6) the sponsor states:

> *Importantly, the Protocol Agreement does not specifically mention lesions from the 3-month follow-up arm, referred to as the F6 population in the Study Protocol. In Figure 6 (see Attachment 4) of Study Protocol 20061 (previously Protocol 20031, see Attachment 5 – Document applying Protocol Agreement to Protocol 20061), population F3 represents lesions with the pre-biopsy clinical diagnosis "Melanoma cannot be ruled out." Populations F4 and F7 represent lesions with the pre-biopsy clinical diagnosis "Not melanoma." Population F7 consists of pigmented lesions without any clinical or historical characteristics of melanoma and is not, therefore, the intended use population for MelaFind. Population F4 consists of two subpopulations: F5 are lesions scheduled for biopsy that were enrolled in the biopsy arm of the pivotal trial and F6 are lesions scheduled for 3-month follow-up. In this Figure, F6 lesions are clearly designated to be "Off Study," that is, these lesions are not eligible for primary endpoint analysis, and as such, are not to be used to evaluate the safety and effectiveness of MelaFind®....*
>
> *Thus, according to Protocol 20061, F6 lesions were not eligible for the primary analyses, even after biopsy. The pivotal trial Protocol 20061 states that:*
>
> > *"Cutaneous lesions examined with MelaFind must satisfy all of the following inclusion criteria: ...*
> > *2) Clinical management of the lesion by the examining dermatologists is either:*
> > > *-- Biopsy of the lesion in toto,*
> > > *-- OR –*
> > > *-- 3-month follow-up of the lesion"*
>
> *Thus, the Study Protocol specified populations F3 and F5 (biopsy of the lesion in toto) to be eligible and, according to the Protocol Agreement, appropriate for primary analysis, contrary to the statement of the letter from the FDA dated March 10, 2010. The 3-month follow-up arm of the study was always optional for investigators, and was not required* (ref: May 7, 2010 Response Letter).

6 – FDA Review Team's Response to the Sponsor's Feedback:
Based upon the results of Protocol 20061, the FDA review team has the following concerns on whether the sponsor met Point 1 (exclusion of F6 Group) of the Protocol Agreement and their revision of their proposed indications for use to include MelaFind use on all atypical lesions:

- All enrolled atypical lesions suspicious for melanoma in Protocol 20061 were biopsied by dermatologists. Patients were not enrolled based upon the criteria to

follow-up in 3-months, that is, with final decision to not biopsy at the time of presentation.

- All lesions enrolled in Protocol 20061 were atypical for suspicion for melanoma (F1). They were then re-categorized based upon their clinical impression of "Melanoma" (F2), "Melanoma cannot be ruled-out" (F3), and "Not Melanoma" (F4). However, criteria for this re-categorization have not been defined. Re-categorization resulted in patient group F5, who were enrolled to have a lesion biopsied in toto though the dermatologist suspected that the lesion was not melanoma.
- The subgroup 'Not Melanoma" (F4) is included within the group where the lesions were biopsy in toto. This group does not appear to substitute for patients considered *not suspicious* for biopsy and does not represent the overall atypical lesion population for *when a final decision to biopsy has not been made by the study physician* since this atypical lesion population was initially screened for suspicion of melanoma.

7 – The Sponsor Provides Protocol 20063 in Response to FDA Review Team's Concerns:

To address the FDA review team's concerns that the clinical data from Protocol 20061 has not demonstrated that MelaFind may be used on all atypical lesions (suspicious and non-suspicious for melanoma) rather than just atypical lesions suspicious for melanoma, the sponsor is using the results from Protocol 20063 to demonstrate that MelaFind may be used on all atypical lesions (suspicious and non-suspicious for melanoma)..

In Protocol 20063, non-study investigators of Protocol 20061 evaluated a random subset of lesions from Protocol 20061 to determine whether or not they would make the decision to biopsy. Thus, the sponsor is concluding from lesion management standard of care, that if a lesion is to be biopsied it is suspicious for melanoma, and if they are not biopsied it is not suspicious for melanoma. Results of the study investigators in Protocol 20063 demonstrated that their biopsy sensitivity of atypical lesions suspicious of melanoma was 72% compared to the 100% biopsy sensitivity of Protocol 20061. The sponsor is concluding that because these atypical lesions were from the MelaFind trial, some of the lesions that were biopsied by the study dermatologists would not be considered suspicious for melanoma and, therefore, would not be biopsied by some non-study investigators. The sponsor concludes this heterogeneity in the threshold of suspicion for melanoma, and, as a result, of biopsy decisions among dermatologists, demonstrates that population in the MelaFind study represents the population of all atypical lesions (suspicious and non-suspicious for melanoma).

8 – FDA Review Team's Concern's with Protocol 20063:

- Protocol 20063 was not part of the in the Protocol Agreement items. Only data from Protocol 20031 (later amended for Protocol 20061) was proposed during the Protocol Agreement.
- The lesions studied in Protocol 20063 were from the same lesions in Protocol 20061 and this does not address the issue of MelaFind's performance on all atypical lesions (suspicious and non-suspicious for melanoma) since these

atypical lesions were already selected in Protocol 20061 for suspicion of melanoma.

- The evaluation of atypical pigmented lesions by dermatologists or other health practitioners to decide which lesion should be biopsied or excised *in toto* requires a detailed patient history including personal and family history of atypical pigmented lesions or melanoma as well as a full examination of the patient and including a global view of pigmented lesions and their pattern. Regardless of their number or their resolution, digital picture sets of individual pigmented lesions would not convey all the clinical information that a dermatologist would gather while directly examining a patient with pigmented lesions in an office setting. If given the choice, a practicing dermatologist would generally prefer to use the option of full history and direct patient examination over the option of examining digital pictures of a specified lesion along with the patient history in rendering their decision. Thus, Protocol 20063's study design does not really replicate or match Protocol 20061's study design and does not appear to support the conclusion that heterogeneity of atypical lesions suspicious for melanoma and biopsy decisions exist in the atypical lesion population of Protocol 20061.
- The extent to which the 10% subset represents the overall population and the effect of second re-categorization by readers has not been presented. Data have not been presented stratified for lesions deemed for 'not biopsy' compared to 'for biopsy' by 20063 reader physicians to allow comparison of 20061 and 20063.

VII – FDA Review Team's Clinical and Statistical Analysis

1.1 – Study Population of Protocol 20061:

The lesions enrolled in Protocol 20061, were atypical lesions that were initially screened by the examining dermatologist to be suspicious of melanoma. Since all atypical lesions enrolled were deemed to be suspicious, they were all biopsied in toto.

1.2 – Proposed Lesion Population for MelaFind Use:

Though the device has been only studied on atypical lesions suspicious for melanoma, the sponsor is proposing to use MelaFind on all atypical lesions (suspicious and non-suspicious for melanoma).

1.3 – Potential Clinical Concerns with Proposed Lesion Population for MelaFind Use:

MelaFind, in Protocol 20061, was only applied to atypical lesions suspicious for melanoma by the examining dermatologist, thus, there is a possibility that MelaFind has not been used on all atypical lesions that are suspicious and non-suspicious for melanoma. Protocol 20063 further confirmed that the dermatologists vary among themselves in calling an atypical lesion suspicious for melanoma, thus, by studying only atypical lesions suspicious for melanoma by the Protocol 20061's dermatologists, some atypical lesions not suspicious for melanoma might have been missed. The only lesions in Protocol 20061 are those that were considered atypical suspicious lesions for melanoma by the examining dermatologist. Protocol 20063 indicates that other physicians may not consider some of these atypical lesions suspicious for melanoma. For this reason, the sponsor wants to propose MelaFind use to all atypical lesions, including those non-suspicious for melanoma.

However, Protocol 20061 may have included only a subset of all atypical lesions considered suspicious by some dermatologists. Depending on the expertise level of the examining dermatologist of Protocol 20061, it is possible that a number of atypical lesions may not have been included in the study if the investigators in Protocol 20061 represent an upper level of expertise. That is, atypical lesions that a less experienced dermatologist might consider suspicious may not have been not included in Protocol 20061. The number of such lesions may be substantial. The performance of the device on these atypical lesions is unknown and could be worse (or at least different) than on those studied.

In regards to MelaFind being used on all atypical lesions, the sponsor states that the intended use population was studied in Protocol 20061 since their proposed indications use states, *MelaFind® is indicated for the evaluation of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling"),* which is represented by the lesions in Protocol 20061. However, the examining dermatologist

initially screened the lesion for suspicion of melanoma, and it is possible that the enrolled lesions may have more than one characteristic of being atypical depending upon the expertise of the examining dermatologist (see above discussion). This could potentially enrich the population of lesions with potentially more melanomas than might be found in all atypical lesions. Thus, the FDA review team believes the atypical lesion population studied in Protocol 20061 may only be a subset of the atypical lesion population targeted in the proposed indications for use. In addition, if the sponsor is proposing that the atypical lesions studied in Protocol 20061 had lesions with only one characteristic of being clinically atypical, the FDA review team believes some of those atypical lesions having one characteristic of being clinically atypical could have appeared in the 3-month follow up group (F6) due to clinical lesion management and may not have been biopsied in toto.

1.4 – Potential Statistical Concerns with Proposed Lesion Population for MelaFind Use:

To the extent that MelaFind diagnostic performance has not been evaluated on all atypical lesions (suspicious and non-suspicious for melanoma), its Sensitivity, Specificity, Positive Predictive Value (PPV) and the Negative Predictive Values (NPV) can be biased for this population. MelaFind diagnostic performance in Protocol 20061 may be biased relative to this population because its performance may differ for atypical lesions included in the study (i.e., those suspicious for melanoma) than for atypical lesions not included in the study (i.e., those not suspicious for melanoma). The set of atypical lesions suspicious for melanoma included in Protocol 20061 were based on assessments by board-certified dermatologists. Physicians less experienced than these dermatologists may have selected a different set of lesions, or perhaps a larger set, suggesting further that the set of atypical lesions included in Protocol 20061 may not be representative of all atypical lesions.

Additionally, PPV and NPV are subject to additional bias because they depend on prevalence as well as Sensitivity and Specificity. The prevalence of melanoma is likely inflated among atypical lesions included in the study, i.e., the atypical lesions suspicious for melanoma. As stated in the paper by Soon et al[5], an excellent test, defined by its sensitivity and specificity, may have poor positive predictive value when used in patients with a low pre-test probability (i.e., prevalence). MelaFind may be expected to have a poorer PPV than given by the study if it is used on a population of atypical lesions (suspicious and non-suspicious for melanoma) that is not enriched with atypical lesions suspicious for melanoma.

The predicament of estimating MelaFind diagnostic performance from the study is illustrated by stratifying test results by true disease status as shown on the next page:

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5 Soon SL *et al*. Computerized Digital Dermoscopy: Sensitivity and Specificity Aren't Enough. Letter: J Investigative Dermatology 2003;121:214-215.

		Disease (Melanoma) Clinical Diagnosis			Not Disease (Not Melanoma) Clinical Diagnosis		
		+	-	total	+	-	total
Mela	+	a1	[b1]		a2	[b2]	
Find	-	c1	[d1]		c2	[d2]	
Total		n_{1D}	[n_{2D}]	[n_D]	$n_{1D'}$	[$n_{2D'}$]	[$n_{D'}$]

The clinical diagnosis is +ve if the clinician recommended biopsy and it is –ve if the clinician recommended not to biopsy. The values in the cells a1, c1, a2, c2, $n_{1D,}$ $n_{1D'}$ are observed in the study, but the values in the cells [b1], [d1], [b2], [d2] may have been under counted if not all atypical lesions yielding a –ve clinical diagnosis were studied. Consequently, [n_{2D}], [$n_{D'}$], [$n_{2D'}$], [n_D] would also have been under counted, which, in particular, affects the denominators [$n_{D'}$] and [n_D] for Sensitivity and Specificity. Therefore, the estimates of both sensitivity ((a1+ [b1])/ [n_D]) and specificity ((c2 + [d2])/ [$n_{D'}$]) can be biased if not all atypical lesions (suspicious and non-suspicious for melanoma) were studied and MelaFind diagnostic performance may be different on these missing lesions than for those included in Protocol 20061.

In order to get unbiased estimates of sensitivity and specificity of MelaFind the FDA review team needs at least a random sample from the clinically negative lesions and to keep track of the sampling fraction. Protocol 20061 may not have had any lesion from such a group.

1.5 – FDA Review Team's Conclusion:

The diagnostic performance of MelaFind, as estimated in Protocol 20061, may not be representative of its performance in the population of all atypical lesions (suspicious and non-suspicious for melanoma) when assessed by a physician other than a board-certified dermatologist. The reason is that Protocol 20061 included only atypical lesions suspicious for melanoma, where the lesions were from patients examined by the dermatologist who determined the level of suspicion.

2.1 – Performance of Protocol 20061:
From the data of 20061 which studied atypical lesions suspicious for melanoma, and the intent of the Protocol Agreement to rule-out melanoma, and assuming that the "pre-biopsy diagnoses are accurate to form "Melanoma Cannot be Determined" (F3) and "Not Melanoma"(F4), sub-groups, we can compare MelaFind Diagnostic Performance to the examining dermatologists.

FDA Review Team's Analysis of Results:

Analysis was completed on the F3 and F4 populations due to Point 3 of the Protocol Agreement:

> *The population (F3 and F4 in figure 4 on page 16) of lesions/patients that will be included in the primary analysis - i.e., lesions receiving clinical diagnoses of*

"Melanoma cannot be ruled-out" and "Not melanoma" - are appropriate for evaluating the sensitivity and specificity of MelaFind when a final decision to biopsy has not been made by the study physician.

Note that a Dermatologist outcome is positive if the lesion was determined as either "Melanoma" or "Melanoma cannot be ruled out" and it was negative if the examiner called it "Not Melanoma".

Table 8: MelaFind Diagnostic Performance for sub-groups "Melanoma cannot be Ruled Out" (F3) and 'Not Melanoma" (F4) with positive reading as MM

	Dermatohistopathology		
MelaFind	*MM	Not MM	Total
Positive	112	1339	1451
Negative	2	158	160
Total	114	1497	1611

*Melanoma (MM)

Sensitivity=98.25% (112/114) (95% CI: 93.8% to 99.8%)[5]
Specificity=10.55% (158/1497) (95% CI: 8.9% to 12.2%)[6]
LR(+)=sensitivity/(1-specificity)=0.9825/(1-0.1055)=1.10
LR(-)=(1-sensitivity)/specificity=0.0175/0.1055=0.17
Prevalence= 7.07% (114/1611)
PPV=7.72% (112/1451)
NPV=98.75% (158/160)

[5] The 95% two-sided confidence interval was calculated using Clopper-Pearson exact method.

[6] The 95% two-sided confidence interval was calculated by bootstrap method to account for multiple lesions from same patient.

Biopsy Ratio (1339/112):1 or 12.0:1

Table 9: Dermatologist Diagnostic Performance for sub-groups "Melanoma cannot be Ruled Out" (F3) and 'Not Melanoma" (F4) with positive reading as MM

	Dermatohistopathology		
Dermatologist	*MM	Not MM	Total
Positive	113	1415	1528
Negative	1	82	83
Total	114	1497	1611

*Melanoma (MM)

Sensitivity=99.12% (113/114) (95% CI: 95.2% to 100.0%)[7]
Specificity=5.48% (82/1497) (95% CI: 4.41% to 6.80%)[7]
LR(+)=sensitivity/(1-specificity)=0.9912/(1-0.0548)=1.05
LR(-)=(1-sensitivity)/specificity=0.0088/0.0548=0.16
Prevalence= 7.07% (114/1611)
PPV= 7.4% (113/1528)

NPV= 98.8% (82/83)
[7]The 95% two-sided confidence interval was calculated using Clopper-Pearson exact method.

Biopsy Ratio (1415/113):1 or 12.5:1

The biopsy ratio of MelaFind was 12.0:1 while the dermatologist was 12.5:1.

biopsy ratio = number of false positive biopsies/number of true positive biopsies
number of false positive biopsies = biopsies of lesions that are negative for disease
number of true positive biopsies= biopsies of lesions that are positive for disease.

If Melanoma (MM), High-Grade Dysplastic Nevi (HGDN), Atypical Melanocytic Proliferation (AMP), and Atypical Melanocytic Hyperplasia (AMP/AMH) are included as MelaFind's positive reading (see page 6), *MelaFind® positive (= 1)*, the following biopsy ratios are provided:

For the MelaFind and Dermatologist Performance for sub-groups "Melanoma cannot be Ruled Out" (F3) and 'Not Melanoma" (F4) with positive reading as MM/HGDN/AMP/AMH:

The biopsy ratio of MelaFind is 8.2:1 to that of the dermatologist was 8.6:1.

(For complete tables of FDA Review Team's Clinical and Statistical Analysis please refer to Appendix 2)

2.2 – FDA Review Team's Conclusion on MelaFind Diagnostic Performance:
In detecting melanoma, MelaFind's diagnostic performance was observed to reduce the number of false biopsies by 76 (158-82) compared to the dermatologist's diagnostic performance at the expense of missing one more true positive (2-1). Specifically, MelaFind's diagnostic performance missed two true positives that the dermatologist's diagnostic performance found and found one true positive that the examining dermatologist did not find, for a net difference of one fewer true positive.

MelaFind did not significantly reduce the number of biopsy ratio (biopsy ratios 12.0:1 to 12.5:1, respectively) when compared to the examining dermatologists. When detecting MM, HGDN/AMP/AMH MelaFind did not significantly reduce the biopsy ratio (8.2:1 to 8.6:1, respectively) when compared to the examining dermatologists. Note that the FDA review team does not believe this is a clinically significant difference. In addition, this difference in biopsy reduction comes at the expense of MelaFind missing one melanoma when compared to the examining dermatologist.

3.1 – Performance of Protocol 20061, when incorporating results of 20063:
The inter-rater variability in 20063 and between 20061 and 20063 with clinically notable difference in lesion categorization for biopsy / not biopsy by physicians within 20063 as well as between physicians in 20061 and 20063, demonstrates that the initial pre-biopsy

diagnosis of the Protocol 20061's atypical lesions into the "Melanoma" (F2), "Melanoma Cannot be ruled out" (F3), and "Not Melanoma" (F4) groups **(Figure 4: Population Schema, pg 14)** would not be categorized in the same manner by other dermatologists. This also implies that the biopsy decisions of each dermatologist will vary, thus, there is no true comparison data of reliable MelaFind performance versus dermatologist lesion management decision making.

Since heterogeneity exists in determining which atypical lesions are suspicious for melanoma and in dermatological biopsy decision making, atypical lesions may be categorized into different "Melanoma Cannot be Determined" (F3) and "Not Melanoma" (F4) groups by different dermatologists. Thus, the device's diagnostic stand-alone performance must be measured by Protocol 20061's complete lesion population.

Note: If MelaFind Diagnostic performance is limited to the lesion population studied in Protocol 20061, atypical lesions suspicious for melanoma, then the true examining dermatologist sensitivity is 100% since biopsy of the lesion means the evaluation is positive and their specificity is 0%.

3.2 – FDA Review Team's Analysis of Results:
The following analysis is the MelaFind's diagnostic stand-alone performance by Protocol 20061's complete lesion population.

Table 10: MelaFind Stand-alone Diagnostic Performance for all lesions selected for the study with positive reading as MM

	Dermatopathology		
MelaFind	*MM	Not MM	Total
Positive	125	1347	1472
Negative	2	158	160
Total	127	1505	1632

*Melanoma (MM)

Sensitivity=98.43% (125/127) (95% CI: 94.4% to 99.8%)
Specificity=10.50% (158/1505) (95% CI: 8.9% to 12.1%)
LR(+)=sensitivity/(1-specificity)=0.9843/(1-0.1050)=1.10
LR(-)=(1-sensitivity)/specificity=0.0157/0.105=0.15
Prevalence= 7.8% (127/1632)
PPV=8.5% (125/1472)
NPV=98.8% (158/160)

Biopsy ratio = 10.8:1

Table 11: MelaFind Stand-alone Diagnostic Performance for all selected lesions in the study population with positive reading as MM/HGDN/AMP/AMH

	Dermatohistopathology		
MelaFind	*MM/HGDN/AMP/AMH	Not MM/HGDN/AMP/AMH	Total
Positive	172	1300	1472
Negative	3	157	160
Total	175	1457	1632

*Melanoma (MM), High-Grade Dysplastic Nevi (HGDN), Atypical Melanocytic Proliferation (AMP), Atypical Melanocytic Hyperplasia (AMP/AMH)

Sensitivity=98.29% (172/175) (95% CI: 95.1% to 99.6%)
Specificity=10.78% (157/1457) (95% CI: 9.1% to 12.4%)
LR(+)=sensitivity/(1-specificity)=0.9829/(1-0.1078)=1.10
LR(-)=(1-sensitivity)/specificity=0.0171/0.1078=0.16
Prevalence= 10.7% (175/1632)
PPV=11.7% (172/1472)
NPV=98.1% (157/160)

Biopsy ratio = 7.6:1

The following dermatologist biopsy ratios are for comparison purposes between MelaFind's diagnostic performance and the examining dermatologist's diagnostic performance from the data in Protocol 20061 and do not reflect future MelaFind use since data regarding how MelaFind will affect clinical decision making on lesion management was not provided.

Biopsy Ratio for Dermatologist's Diagnostic Performance for all lesions in the study with positive reading MM = 11.3:1

Biopsy Ratio for Dermatologist's Diagnostic Performance for all lesions in the study population with positive reading as MM/HGDN/AMP/AMH = 7.9:1

3.3 – FDA Review Team's Conclusion on MelaFind Stand-alone Diagnostic Performance:

From the stand-alone diagnostic performance results of Protocol 20061, when detecting Melanoma, MelaFind missed 2 Melanomas and had 1347 false biopsies. When detecting MM/HGDN/AMP/AMH MelaFind missed 3 MM/HGDN/AMP/AMH and had 1300 false biopsies. The low specificity indicates that MelaFind when used in the atypical lesion population would have a very high false positive fraction (89%) and possibly lower sensitivity than dermatologists, and may increase many unnecessary biopsies from false positive output.

When comparing the biopsy ratios of MelaFind and the examining dermatologist detecting Melanoma, MelaFind's ratio was **10.8:1** and the dermatologist was **11.3:1**. When detecting MM/HGDN/AMP/AMH, MelaFind's ratio was **7.6:1** and the

dermatologist was **7.9:1**. As stated in the analysis of the F3 and F4, population, when looking at the complete atypical lesion population studied in Protocol 20061, the FDA review team does not believe this is a clinically significant difference between MelaFind and the examining dermatologist.

Please see Appendix 2 for additional FDA Review Team's Analysis of Protocol 20063

VIII – FDA Review Team's Summary of Clinical and Statistical Concerns

The following are the outstanding concerns regarding the clinical data from Protocol 20061 and 20063:

1 – Main Concerns:

- This was an observational study. No clinical decisions were made based on MelaFind results. There is no data in Protocols 20061 or 20063 that demonstrates how a dermatologist or other healthcare provider would use the results of the MelaFind. In future use, providers would only have the information on the stand-alone diagnostic performance of the MelaFind results to histopathology diagnoses. There are no data or instructions for use to support the use of MelaFind results in order to actually guide the complex clinical decision to determine when or whether to biopsy or to not biopsy an atypical lesion.
- The FDA review team does not have the data to evaluate what is the risk/benefit (number of unnecessary biopsies to potentially find melanomas) of MelaFind use versus the standard lesion management of care. There is no data to determine the value added for MelaFind use.
- The FDA review team has no data regarding a study testing the capabilities of MelaFind when used by a physician or healthcare professional on an atypical lesion prior to making a decision whether or not the atypical lesions should be biopsied.
- The FDA review team has no data demonstrating that a physician can properly identify atypical lesions for MelaFind use. If this data is not validated, there is potential for physicians to misdiagnose some pigmented skin as atypical lesions. The number of such lesions may be substantial and the performance of the device on these atypical lesions is unknown and could be worse (or at least different) than on those studied.
- Since the device is not 100% sensitive, if use based on the device's diagnostic performance reduces the number of biopsies taken, harm could ensue in the form of missed melanomas. Based on the natural history of some melanomas to spread rapidly – this harm could include fatal outcomes.
- If MelaFind use is limited to atypical lesions suspicious for melanoma, MelaFind's diagnostic performance does not significantly reduce the number of biopsies (12.0:1 to 12.5:1, respectively) when compared to the examining dermatologist's diagnostic performance. This small difference in biopsy reduction comes at the expense of MelaFind's diagnostic performance missing one melanoma when compared to the examining dermatologist's diagnostic performance.
- From the stand-alone diagnostic performance results of Protocol 20061, when detecting MM/ HGDN/AMP/AMH MelaFind missed 3 MM/HGDN/AMP/AMH and had 1300 false biopsies. MelaFind's biopsy ratio was **7.6:1** and the dermatologist was **7.9:1**. FDA does not believe this is a clinically significant difference between MelaFind and the examining dermatologist.
- Clinical concerns for MelaFind use include (but are not limited to) a lack of data to support the proposed Indications for Use, the possibility of missing melanomas

if providers were convinced not to biopsy due the use of the device, the probability of many false positives leading to unnecessary biopsies, the fact that the device has not been shown to reduce the number of biopsies significantly to find melanomas, and a lack of instructions for use for the proposed conditions of use by a physician.

- The FDA review team also believes that the clinical data in Protocol 20061 does not support the proposed indications for use of MelaFind for the detection of early melanoma on *all atypical lesions* since the data is limited to the enrolled atypical lesions suspicious for melanoma.
- The FDA review team also does not believe Protocol 20061 and Protocol 20063 can support MelaFind for its proposed indications for use, *MelaFind® is indicated for the evaluation of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling"),* since the examining dermatologist initially screened the atypical lesion for suspicion of melanoma, making it is possible that the enrolled atypical lesions may have more than one characteristic of being clinically atypical depending upon the expertise of the examining dermatologist. Thus, the FDA review team believes MelaFind may have not been evaluated on all clinically atypical lesions (suspicious and non-suspicious for melanoma) and the atypical lesion population studied in Protocol 20061 is may be a subset of the atypical lesion population targeted in the proposed indications for use.
- Protocol 20063 was not part of the in the Protocol Agreement items. Only data from Protocol 20031 (later amended for Protocol 20061) was proposed during the Protocol Agreement. Furthermore, this study has important potential biases and un-validated assumptions including that the use of photographs of lesions (plus some supportive information on the history of the lesion) has not been demonstrated to be truly comparable to the full history and physical examination of lesions by providers – it may not be able to replicate the information that would be used in a complex clinical decision pathway by the provider to decide whether or not to biopsy an atypical lesion.

The following are some additional concerns the FDA review team has regarding the clinical data of Protocol 20061 and Protocol 20063:

Sponsor's Proposed Indications for Use:
MelaFind® is indicated for the evaluation of clinically atypical cutaneous pigmented lesions (those having one or more clinical or historical characteristics of melanoma, such as asymmetry, border irregularity, color variegation, diameter greater than 6 mm, evolving, patient concern, regression, and "ugly duckling"), when a physician chooses to obtain additional information before making a final decision to biopsy to rule out melanoma. MelaFind® is a non-invasive objective multi-spectral computer vision system designed as a tool to aid physicians in the detection of early (e.g., non-ulcerated, not bleeding, or less than 2.2 cm in diameter) melanoma.

MelaFind® is not a screening device and is not indicated for non-pigmented lesions, banal pigmented lesions, lesions that are clinically identified as definite melanomas, or lesions on special anatomic sites (i.e., acral, mucosal, subungual).

2 – Concerns Regarding Sponsor's Proposed Indications for Use:

- MelaFind use by physicians in their proposed Indications for Use is not supported since MelaFind was designed and powered for board certified dermatologist use, thus, the data provided in this study does not support use for non board-certified dermatologist use.
    - The sponsor intends to educate physicians on selecting the appropriate atypical lesions MelaFind is to be used on.
    - If the FDA review team were to consider approval of use of this device by any physician, then a validated study testing the capabilities of a broader group of physicians in diagnosing atypical pigmented lesions prior to MelaFind use and how MelaFind would be used in such a setting should be included. However, the FDA review team has no data from such a study.
    - If this study is not validated, there is potential for physicians to misdiagnose pigmented skin lesions as atypical lesions, thus, not selecting the appropriate lesion population for MelaFind use. This may result in the increase of unnecessary biopsies of benign lesions, that a board certified dermatologist would have clinically determined to be benign since the selectivity and sensitivity of the MelaFind has not necessarily been determined on these lesions and thus use of MelaFind on these lesions could result in a high number of false positives. Currently, formal training is offered to physicians to become board certified dermatologist and thus be able to diagnose clinically atypical lesions. The FDA review team would have to compare this board certification training to that offered by the sponsor to those physicians operating MelaFind to determine if it is found adequate.
- A claim for detection of early melanoma in their proposed Indications for Use is not supported by the clinical data since MelaFind is intended to provide a diagnostic result of an atypical lesion that has been pre-selected by a dermatologist and does not assist the dermatologist in the early steps of diagnosing pigmented skin lesions on a patient. MelaFind is not solely aimed at detecting early melanoma, but also lesions such as high-grade dysplastic nevus (dysplastic nevus with severe atypia), and atypical melanocytic proliferation/hyperplasia. The FDA review team believes the sponsor should specify the lesions MelaFind detects in regards to the device's positive detection algorithm of atypical lesions included in Protocol 20061.
- MelaFind was studied on non-acral (palmar and plantar lesions were excluded), non-ulcerated and non-bleeding pigmented cutaneous lesions that have diameter 2-22mm and are atypical due to at least one clinical characteristic of melanoma such as asymmetry, border irregularity, color variegation, regressing, evolving overtime, is causing patient concern or is an 'ugly duckling.' *Note: The panel will*

be asked to discuss the appropriate atypical population MelaFind may be used on since the lesion population was initially screened for suspicion of melanoma.

- No data of MelaFind use on amelanotic lesions even though these lesions are considered clinically atypical. The sponsor's identification of atypical cutaneous pigmented lesions in the proposed Indications and Usage statement for MelaFind could still include these atypically pigmented (e.g. pheomelanin vs. darker melanin) lesions.
- Data is limited to the atypical pigmented lesions of the white patient population since these constituted 98% of the data (Please see table on page 17).
- Any scarring was excluded from the clinical studies. Atypical melanomas in the setting of scarring is a relevant clinical issue where MelaFind's limitations are not adequately identified.
- A claim that MelaFind is "a tool to aid in the detection of early melanoma for physicians" in their proposed Indications for Use may be misleading and is not appropriate here since MelaFind has the capability of rendering what could be interpreted to be diagnosis, just like a physician would. MelaFind provides a binary output, positive (MelaFind=1) and negative (MelaFind=0).
    - The clinical data did not address the effect of clinical decision on lesion management, and there is no data or instructions for use to support the use of MelaFind results to guide clinical decision to determine when to biopsy or to not biopsy an atypical lesion. Thus, the FDA review team does not have the data to truly evaluate what the risk/benefit (number of unnecessary biopsies to potentially find melanomas vs. that of the demonstrated evidence that it may miss melanoma) of MelaFind use versus the standard lesion management of care.
- The sponsor's claim that MelaFind may be used on atypical lesions for *when a final decision to biopsy has not been made by the study physician* does not appear to be supported by the inclusion of the subgroup 'Not Melanoma" (F4) since all atypical lesions included within this group were biopsied in toto. This group may not be able to substitute for patients considered *not suspicious* for biopsy. This does not represent the overall atypical lesion population for *when a final decision to biopsy has not been made by the study physician* since this atypical lesion population was initially screened for suspicion of melanoma.

The FDA review team will ask the Panel to discuss the proposed indications for use.

3 – Protocol Agreement Concerns:

- By not providing the 3-month follow up group (F6), the FDA review team have determined that the sponsor has not met Point 1 of the Protocol Agreement, since that group would have provided additional clinical data to evaluate whether MelaFind was able to effectively rule-out melanoma from the "Not Melanoma" (F4) Group by comparing the MelaFind result to the dermatologist's decision to defer immediate biopsy for a 3 month follow-up. The FDA review team and the sponsor would have had additional data to help determine if MelaFind could safely and effectively rule-out melanoma to reduce unnecessary biopsies in atypical lesions suspicious of melanoma.

- The FDA review team have determined that the data presented in Protocol 20061 cannot support Point 3 of the Protocol Agreement, *when a final decision to biopsy has not been made by the study physician.* The subgroup "Not Melanoma" (F4) cannot substitute for patients considered *not suspicious* for biopsy and does not represent the overall atypical lesion population for *when a final decision to biopsy has not been made by the study dermatologist.*
- By not meeting the terms of the Protocol Agreement in the conduct of this study (which was not conducted under IDE), the Protocol Agreement's conditions have not been met. These are also substantial scientific issues essential to determining the safety or effectiveness of the device.

4 – MelaFind Performance Concerns:

- If we assume the conclusions from Protocol 20063, heterogeneity among dermatologist's suspicion of melanoma, this demonstrates that the initial pre-biopsy diagnosis of the Protocol 20061's atypical lesions into the F2, F3, and F4 groups would not be categorized in the same manner by other dermatologists, which questions the validity of the statistical analysis of Protocol 20061's lesion population.
- Implies that the biopsy decisions of each dermatologist will vary, thus, there is no comparison data of reliable MelaFind performance versus dermatologist lesion management decision making.
- Due to this heterogeneity, MelaFind stand-alone diagnostic performance must only be considered among the atypical lesions suspicious for melanoma selected in Protocol 20061. However, it is possible that atypical lesions that a less experienced dermatologist might consider suspicious were not included in Protocol 20061, thus, some atypical lesions might not have been studied by MelaFind since they were not originally included in Protocol 20061. The number of such lesions may be substantial and the performance of the device on these atypical lesions is unknown and could be worse (or at least different) than on those studied.
- In Protocol 20061, since atypical lesions were screened for suspicion, it is possible the prevalence is inflated and that MelaFind diagnostic performance has not been evaluated on all atypical lesions (suspicious and non-suspicious of melanoma) which would bias the Sensitivity, Specificity, Positive Predictive Value (PPV) and the Negative Predictive Values (NPV).
- The MelaFind diagnostic performance may have a different predictive value (possibly poorer positive predictive value) if used on a population of atypical lesions that are not enriched with atypical lesions suspicious for melanoma.

5 –Summary of Concerns:

FDA's Mission is to Protect and Promote the Public Health and the FDA review team has significant concerns this device has not been studied adequately for its current indications for use and therefore puts the health of the public at risk.

The FDA review team, as this Executive Summary explains in detail, does not believe that the current studies (which include an important deviation from the protocol agreement) have demonstrated any true additive value of using MelaFind on atypical lesions (suspicious and non-suspicious of melanoma) in the clinical decision process, as they are to be dealinated in the indications for use, to be biopsied at an acceptable trade off of risk versus benefit. The current data demonstrates that in the primary study, Protocol 20061, board-certified dermatologist's diagnostic performance actually demonstrated a slightly higher sensitivity than MelaFind's diagnostic performance in 114 lesions that turned out to be melanoma. Moreover the study data suggests, regarding the diagnostic performances, that both the dermatologists and the device would theoretically have biopsied about 11 atypical false positive lesions to find an actual melanoma among the study lesions (with the caveat that these lesions were already screened for suspicion of melanoma); but rather than demonstrating a positive theoretical utility, based on the current data, the device could have contributed to a clinical decision to not biopsy a melanoma - that otherwise would have been biopsied and may increase many unnecessary biopsies due to high false positive output.

Furthermore, the sponsor has not provided an acceptable study for the device's proposed indications for use since there is a possibility the device has not been studied on all the atypical lesions (suspicious and non-suspicious of melanoma) covered in the indications for use. The FDA review team does not believe Protocol 20063 can support the use of MelaFind to be used on all atypical lesions (suspicious and non-suspicious of melanoma) since it cannot replicate the prospective study of Protocol 20061 to make a lesion management decision since study investigators looked at photographs and case histories of the atypical lesion rather than examining the patient as in Protocol 20061. In addition, Protocol 20061's atypical lesion population may have been limited due to the initial screening for suspicion of melanoma. Protocol 20063 is also a study with multiple potential biases that are covered above and will be reviewed in the panel session.

In regards of MelaFind being used by a physician or healthcare professional on atypical lesions prior to making a decision whether or not the atypical lesions should be biopsied, The FDA review team has no data regarding a study testing the capabilities of MelaFind with such group. In addition, the sponsor has provided no data demonstrating that a physician can properly identify atypical lesions for MelaFind use. If this data is not validated, there is potential for physicians to misdiagnose some pigmented skin as atypical lesions. The number of such lesions may be substantial and the performance of the device on these atypical lesions is unknown and could be worse (or at least different) than on those studied.

As such, and since melanoma is often a fatal disease and the standard of care[6] is to seek early detection and biopsy on any suspicious lesion - this device has not with the current data demonstrated any true clinical trade off and may potentially cause more harm than good to the health of the public. The FDA review team does not believe Protocol 20061

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6 Rigel, D. S., Russak, J. R., and Friedman, R., The Evolution of Melanoma Diagnosis: 25 Years and Beyond the ABCDs, *CA Cancer J Clin* 2010;60;301-316;

or Protocol 20063 can be a proxy for a new validated study that would try to actually ascertain prospectively how dermatologists and/or other providers would use the device to help actually select an atypical lesion in practice and what is the actual risk/benefit of the device in the biopsy decision making process in practice.

The FDA review team sees both studies as serving as exploratory studies for the actual risk benefit of this device, and recommends a new primary study for the actual indications for use of the device. With this background, we will be asking for the panel to provide formal input on a series of questions related to these points.

The FDA review team will ask the Panel to discuss the concerns dealing with MelaFind performance and the uncertainty of the data.

In addition, the FDA review team will ask the panel to address the level of expertise needed to effectively and safely select lesions for use with MelaFind.

Labeling

Note to Panelists: *The inclusion of a section on labeling in this memo should not be interpreted to mean that the FDA review team has made a decision or is making a recommendation on the approvability of this PMA device.* The Labeling, including Instructions for Use have not been updated for the revised Indications for Use.

The proposed Instructions for Use are included in the panel pack for your review. Both of these include the following: 1) Description; 2) Indications for Use; 3) Contraindications; 4) Precautions; 5) Instructions for Use; 6) Device Contents; and 7) Summary of clinical study and results.

There is no patient labeling in the PMA application.

The sponsor has included promotional direct-to-consumer advertising in the Panel package.

The FDA review team will ask the Panel to discuss the need for Physician labeling and the adequacy of the patient labeling/Instructions for Use as well as the appropriateness of the direct-to-consumer advertising.

Post-Approval Study:

Note to Panelists: The FDA review team's inclusion of a section on a Post-Approval Study (PAS) in their Executive Summary should not be interpreted to mean that the FDA review team has made a decision or is making a recommendation on the approvability of this PMA device. The discussion of a post-approval study plan does not in any way alter the requirements for premarket approval. A recommendation from the Panel on whether the data demonstrates reasonable assurance on device safety and effectiveness must be based solely on the premarket data. The issues noted below are the FDA review team's comments regarding potential post-approval stu

The applicant did not provide a post-approval study (PAS) plan in the PMA. The applicant reported that there were no device-related adverse events in the pivotal trial. Based on the limitations of the PMA clinical data, at this time, the FDA review team has not identified specific questions that could be addressed in a Post-Approval Study. *The FDA review team will ask the Panel to comment on the need for a post-approval study if MelaFind were to be approved.*

Literature:

The following literature was reviewed by the FDA review team and will be provided in full-text in the Panel Pack for the panelists:

1. Rigel, D. S., Russak, J. R., and Friedman, R., The Evolution of Melanoma Diagnosis: 25 Years and Beyond the ABCDs, *CA Cancer J Clin.* 2010;Vol.60;301-316.
2. NIH Consensus Statement, Diagnosis and Treatment of Early Melanoma, NIH Development Conference. 1992, Vol. 10; 1
3. Abbasi, N. R., Shaw, H. M., Rigel, D. S., et al., Early Diagnosis of Cutaneous Melanoma: Revisiting the ABCD Criteria, JAMA. 2004; Vol.292;22;2771-2776.
4. Balch, C. M., Gershenwald, J. M., et al., Final Version of 2009 AJCC Melanoma Staging and Classification, Journal of Clinical Oncology. 2009;Vol.27;36;6199-6206.
5. Divito, S. J., Ferris, L. K., Advances and short comings in the early diagnosis of melanoma, Melanoma Research. 2010;Vol.00;00;1-9.
6. Robinson, J. K., Turisi, R., Skills Training to Learn Discrimination of ABCDE Criteria by Those at Risk of Developing Melanoma, Arch Dermtol. 2006;Vol.142;447-452.